REMARKS

Claims 1-14 and 17-34 were pending in the application. Claims 2, 3, 13, 14, 17, 18, 19, and 27-34 have been amended and claims 1, 6-12, 15, 16, and 24-26 have been canceled, without prejudice. Accordingly, upon entry of this amendment, claims 2, 3, 4, 5, 13, 14, 17, 18, 19, 20, 21, 22, 23, and 27-34 will be pending. Claims 13 and 14 have been updated to reflect amendments made to the claims in the Preliminary Amendment filed on August 24, 2001. Claims 13-14, and 28-34 have been amended to include all of the limitations of the base claim and any intervening claims. Claims 2, 3, 18, 19, and 27 have been amended to alter dependency. Thus, the above amendments raise no new issues which would require further consideration and/or search by the Examiner.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication that claims 13-14 and 28-34 are objected to as being dependent up on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants respectfully submit that claims 13-14, and 28-34 have been amended to include all of the limitations of the base claim and any intervening claims, and, thus, should be allowable.

Withdrawal of Objections and Rejections

Applicants gratefully acknowledge the Examiner's indication that the objection to the disclosure regarding Figure 8 is withdrawn. In addition, Applicants acknowledge the Examiner's indication that the written description rejection to the phrase "substantially complementary" is withdrawn, the written description rejection regarding "labeling" is withdrawn, the new matter rejection of the phrase "from an immunoglobuilin heavy chain" is withdrawn, and the enablement rejection addressing "a library of candidate agents" is withdrawn.

Rejection of Claims 1-2, 9, 18-23, and 27 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-2, 9, 18-23 and 27 under 35 U.S.C. 102(b) "as being anticipated by Berton et al. PNAS USA Vol. 86 (April 1989) pages 2829-33." In particular, the Examiner is of the opinion that

> Berton et al. teach a method for determining whether a candidate agent is capable of modulating germ line transcription (e.g. of lgG1) by: adding a "candidate agent" (e.g. interleukin 4 or interferon gamma as "small peptide molecules") to a "plurality of cells" (e.g. lipopolysaccharide-stimulated B cells) using an "RNAse protection assay" e.g. antisense probes to mRNA from the immunoglobulin heavy chain gene locus of lgG1 and quantifying the amount of germline mRNA to a control after the addition of RNAse See. e.g. Abstract; pages 2829-2830; Figures 1-4. It is noted that the means of producing the "candidate agent" (e.g. present claims 20-23) is not given patentable weight since the claim limitations amount to claiming the use of a product (e.g. candidate agent) by its means of manufacture (e.g. product by process).

Applicants respectfully traverse the foregoing rejection and reiterate their remarks made in the Amendment and Response filed on December 23, 2003.

Berton *et al.* fail to teach or suggest each and every limitation of the claimed invention. Claims 13, 14, and 28-34 are directed to methods for determining whether a candidate agent is capable of modulating germline transcription, comprising adding a candidate agent to a plurality of cells, preparing mRNA from said plurality of cells to form an mRNA mixture, adding to said mixture at least a first RNAse protection probe (RPP) substantially complementary to a first germline mRNA from an immunoglobulin heavy chain gene locus to form a first hybridization complex between said first germline mRNA and said first RPP, ***wherein said RPP has a sequence selected from the group consisting of SEQ ID NOs:1-13,*** adding an RNAse protection enzyme (RPE) to said mixture, such that mRNA that is not protected is digested; and quantifying the amount of said first germline mRNA as compared to a cell in the absence of a candidate agent, to thereby identify a candidate agent that alters the amount of said first germline mRNA.

Berton *et al.* teach the use of an RNase protection assay to demonstrate that IL-4 induces expression of germ-line γ1 transcripts in small, resting B cells, but lipopolysaccharide enhances expression (see abstract). Berton *et al.* fail to teach or suggest the claimed methods wherein the ***RPP has a sequence which is selected from the group consisting of SEQ ID NOs:1-13***. Berton

et al. also fails to teach or suggest these methods further comprising stimulating cells to produce germline mRNA as is claimed in claim 2. In addition, Berton *et al.* also fail to teach or suggest the claimed methods wherein the candidate agent is a small molecule or a peptide, as is claimed in claims 18-23. Berton *et al.* also fail to teach or suggest the claimed methods wherein the first RNAse protection probe and the first germline mRNA contain less than 5 base mismatches, as is claimed in claim 27. Therefore, Berton *et al.* fail to teach each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, claims 1 and 9 have been canceled, thereby rendering the foregoing rejection moot with respect to these claims.

With respect to claims 2, 18-23 and 27, Applicants respectfully submit that these claims are dependent upon claims 13, 14, or 28-34, which have been rewritten in independent form including the base claims and any intervening claims, and therefore should be allowable, as indicated by the Examiner in the instant Office Action.

Rejection of Claims 1-2, 8-12, 17-23 and 27 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-2, 8-12, 17-23 and 27 under 35 U.S.C. §103(a) as being unpatentable over Berton et al. PNAS USA Vol. 86 (April 1989) pages 2829-33. In particular, the Examiner is of the opinion that

> the Berton et al. reference specifically teaches that T cell-derived lymphokines (e.g IL-4 and/or interferon gamma) are known to play an important role in the regulation (e.g. induction/suppression of expression) of immunoglobulin isotype switching with regard to all of the IgG isotype species (e.g. lgG1-G4) as well as IgE (e.g. see page 2829, especially left column) and abstract. Accordingly, one of ordinary skill in the art would be motivated to further apply the Berton et al. reference method utilizing an RNAse protection assay (including making the corresponding antisense probes) as it applies to the T cell derived lymphokines (e.g. IL-4 and/or interferon gamma) in order to evaluate the effect of these cytokines on isotype switching as it relates to IG2-4 or IGE.

Applicants respectfully traverse the foregoing rejection and reiterate their remarks made in the Amendment and Response filed on December 23, 2003.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations*** (M.P.E.P. 2143).

The teachings of Berton *et al.* are set forth above. Berton *et al.* fail to teach or suggest the claimed methods wherein ***the RPP has a sequence which is selected from the group consisting of SEQ ID NOs:1-13***, as is claimed in independent claims 13, 14, and 28-34. Berton *et al.* also fail to each or suggest these methods further comprising stimulating cells to produce germline mRNA, as is claimed in claim 2. Furthermore, Berton *et al.* does not teach or suggest the claimed methods further comprising adding to said mixture ***at least a second RPP substantially complementary to a second germline mRNA to form a second hybridization complex between said second germline mRNA and said second RPP***; and quantifying the amount of said second germline mRNA as compared to a cell in the absence of a candidate agent to thereby identify a candidate agent that alters the amount of said first germline mRNA but not said second germline mRNA, as is set forth in claim 17. Berton *et al.* also fail to teach or suggest the claimed methods wherein the candidate agent is a small molecule or a peptide, as is claimed in claims 18-23. Lastly, Berton *et al.* fail to teach or suggest the claimed methods wherein the first RNAse protection probe and the first germline mRNA contain less than 5 base mismatches, as is claimed in claim 27.

In view of the foregoing, Applicants respectfully submit that the claimed invention is not obvious over the art of record. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, claims 1 and 8-12, have been canceled, thereby rendering the foregoing rejection moot as it pertains to these claims. With respect to claims 2, 17-23 and 27, Applicants respectfully submit that these claims are dependent upon claims 13, 14, or 28-34, which have been rewritten in independent form including the base claims and any intervening claims, and therefore should be allowable, as indicated by the Examiner in the instant Office Action.

Rejection of Claims 1-3, 5-12, 17-23 and 27 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 5-12, 17-23 and 27 under 35 U.S.C. §103(a) as "being unpatentable over Berton et al. PNAS USA Vol. 86 (April 1989) pages 2829-33 and Turaga et al. J. Immunol. Vol. 151 (3) (Aug. 1993) pages 1383-1390." In particular, the Examiner is of the opinion that

> [t]he Berton et al. reference method differs from the presently claimed invention by failing to: a. additionally exemplify the utilization of the RNAse protection assay (with a second or greater different probes: see claim 17) to screen the ability of interleukin 4 or interferon gamma on other immunoglobulin IgG isotypes (E.g. lgG2-4: claims 10-12), IgA (claims 6-7) or IgE (claim 8); and b. teach a labeled (e.g. radio isotopic) probe (e.g. claims 3 and 5). Regarding item a. above, the Berton et al. reference specifically teaches that T cell-derived lymphokines (e.g. IL-4 and/or interferon gamma) are known to play an important role in the regulation (e.g. induction/suppression of expression) of immunoglobulin isotype switching with regard to all of the IgG isotype species (e.g. lgG1-G4) as well as IgE (e.g. see page 2829, especially left column) and abstract. Additionally, Turaga et al. teach that "Transforming growth factor beta selectively induces IgA." (see Turaga et al. page 1383, left column).

Applicants respectfully traverse the foregoing rejection and reiterate their remarks made in the Amendment and Response filed on December 23, 2003.

As set forth above, Berton *et al.* teach the use of an RNase protection assay to demonstrate that IL-4 induces expression of germ-line γ1 transcripts in small, resting B cells, but lipopolysaccharide enhances expression (see abstract). Berton *et al.* also state that IL-4 induces

the expression of IgG1 and IgE and suppresses the expression of IgM, IgG3, and IgG2 in mitogen-activated B cells.

Berton *et al.* fail to teach or suggest the claimed methods wherein ***the RPP has a sequence which is selected from the group consisting of SEQ ID NOs:1-13***, as is claimed in independent claims 13, 14, and 28-34. Berton *et al.* also fail to teach or suggest the methods of the invention wherein the RPP is labeled, as set forth in claim 3, or wherein the RPP is labeled with a radioisotope, as set forth in claim 5.

Turaga *et al.* teach that "IFNγ selectively induces IgA and IgG3; it also antagonizes IgG1 and IgE enhancement by IL-4." Turaga *et al.* fail to cure the deficiencies of Berton *et al.* as Turaga *et al.* does not teach or suggest the claimed methods of determining whether a candidate agent is capable of modulating germline transcription ***using an RPP comprising a sequence selected from the group consisting of the sequences set forth in SEQ ID NOs:1-13***.

Accordingly, for the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

However, in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejection, claims 1 and 6-12 have been canceled, thereby rendering the foregoing rejection moot as it pertains to these claims.

With respect to claims 2, 3, 5, 17-23 and 27, Applicants respectfully submit that, these claims are dependent upon claims 13, 14, or 28-34, which have been rewritten in independent form including the base claims and any intervening claims, and therefore should be allowable, as indicated by the Examiner in the instant Office Action.

Rejection of Claim 4 Under 35 U.S.C. §103(a)

The Examiner has rejected claim 4 under 35 U.S.C. §103(a) as "being unpatentable over Berton et al. and Turaga et al. as applied to claims 1-3, 5-12, 17-23 and 27 above, and further in view of Chan et al. Analytical Biochemistry Vol. 242 (1996) pages 214-20."

Applicants respectfully traverse the foregoing rejection and reiterate their remarks made in the Amendment and Response filed on December 23, 2003.

Claim 4 is directed to the method of claims 13, 14, or 28-34, wherein the RPP is fluorescently labeled. As set forth above, Berton *et al.* fail to teach or suggest each and every limitation of the claimed invention. Turaga *et al.* fail to cure the deficiencies of Berton *et al.* Chan *et al.* disclose use of a non-isotopic RNAse protection assay using RNA probes that are

dual labeled with biotin and fluorescein for detection. Chan *et al.* fail to cure the deficiencies of Berton *et al.* and Turaga *et al.* in that Chan *et al.* fail to teach or suggest a method for determining whether a candidate agent is capable of modulating germline transcription comprising ***utilizing an RPP comprising a sequence selected from the group consisting of the sequences set forth in SEQ ID NOs:1-13***, as is claimed in the instant invention.

In view of the foregoing, Applicants respectfully submit that the claimed invention is not obvious over the art of record. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

Furthermore, Applicants respectfully submit that claim 4 is dependent upon claims 13, 14, or 28-34. Claims 13, 14, and 28-34 have been amended to include the base claims and any intervening claim, and therefore should be allowable, as indicated by the Examiner in the instant Office Action.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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